27. (New) The composition of Claim 11, wherein the active ingredients of the composition are rapamycin and at least one costimulation blockade agent, wherein the costimulation blockade agent comprises at least one agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.

REMARKS

Restriction Requirement

The Examiner has acknowledged applicants' election of Group II (Claims 11-14) and species B (anti-CD40L antibodies). However, it is not clear whether the restriction of species is final.

With respect to applicant's traversal of the species, the Examiner notes that inventions must be either independent or distinct and a burden on the Examiner if restriction is required. However, although the Examiner has stated that the inventions are distinct, he has not indicated whether there would be a serious burden on the Examiner. Therefore, at this point, applicants have included in the claims the species that applicants believe should be prosecuted with the elected anti-CD40L antibodies. Further clarification from the Examiner is respectfully requested.

Claim Amendments

Claims 11, 13 and 14 have been amended. Claim 11 has been amended to clarify that the claimed composition comprises rapamycin and a biologically active derivative thereof, and at least one costimulation blockade agent. Support for this amendment is found in the Specification on page 3, lines 8-10. Claim 13 has been amended to correct a typographical error; the word "method" was replaced with "composition". Support for this amendment is found in the Specification at page 2, lines 16-24 and page 3, lines 14-16. In addition, Claims 11, 13 and 14 are amended to be drawn to the elected species (anti-CD40L antibodies) and the other species which applicants believe should be prosecuted with the elected species. These amendments were

made for purposes of compact prosecution and not for purposes related to patentability. Support for these amendments is found in the Specification at page 2, lines 16-24 and page 3, lines 14-16.

New Claims 22-27 have been added. Claim 22 is directed to a composition comprising rapamycin, or a biologically active derivative thereof, and at least one costimulation blockade agent comprising at least one agent selected from the group of specific agents set forth in amended Claim 13. Claim 23 is directed to the same composition, further comprising fish oil. Support for these new claims is found in the Specification at page 2, lines 16-24 and page 3, lines 14-16. Support for Claim 23 is additionally found at page 14, lines 13-14. Claim 24 is directed to a kit comprising rapamycin and at least one costimulation blockade agent comprising at least one agent selected from the group of specific agents set forth in amended Claim 13. Support for Claim 24 is additionally found at page 3, lines 13-16.

Claim 25 is directed to a composition consisting essentially of rapamycin and at least one costimulation blockade agent. Claim 26 is directed to a composition consisting of these elements and additional recited elements. Support for these claims is found in the Specification at page 2, lines 16-24; page 3, lines 14-16; and page 12, line 5 to page 14, line 13.

Claim 27 is directed to a composition of Claim 11 wherein the active ingredients are rapamycin and the costimulation blockade agents recited in Claim 11. Additional support for this Claim is found in the Specification at page 12, lines 8-11.

No new matter has been added.

Reference AZW

The Examiner has indicated that the date and page numbers for Reference AZ3 (Wiederrecht et al., Ann. NY Acad. Sci.) are required. The full citation for this reference is: G. Wiederrecht *et al.*, "The Mechanism of Action of FK-506 and Cyclosporin A," *Ann N Y Acad Sci*, 696: 9-19 (1993).

Title

The Examiner has indicated that the title of the invention is not descriptive and that applicants should restrict the title to the claimed invention. Applicants have amended the title as suggested by the Examiner, to state: "Compositions and Kits for Transplant Tolerance".

Formal Drawings

The Examiner has indicated that the Formal Drawings, filed 5/18/98, comply with 37 C.F.R. 1.84. However, the enclosed PTO-948 form indicates that Figure 1 of the Formal Drawings, filed 5/22/00, is objected to under 37 C.F.R. 1.84. Clarification is requested. If necessary, a formal figure will be submitted upon allowance of the claims.

Review of Specification for correction of spelling, trademarks and like errors

The application was reviewed for spelling, trademarks and like errors, and appropriate corrections have been made.

Rejection of Claims 11, 12 and 14 under 35 U.S.C. § 112, First Paragraph

Claims 11, 12 and 14 are rejected under 35 U.S.C. § 112, first paragraph on the grounds that the Examiner believes that the Specification, while being enabling for "costimulation blockade agents and biologically derivatives" consisting of those specific agents set forth in Claim 13 and disclosed in the Specification as filed, does not reasonably provide enablement for any "costimulation blockade agent and biologically active derivative thereof".

According to the Examiner:

> there is insufficient direction or objective evidence as to how to make and how to use any agent which blocks any costimulatory activity (e.g., desired/intended effect of the claimed limitations) for the number of possibilities associated with the myriad of direct and indirect effects associated with various costimulatory pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

For purposes of compact prosecution, applicants have amended the claims to be directed to agents blocking a single costimulatory pathway, namely, costimulation blockade agents selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L, and derivatives thereof. As noted in the Specification, which provides guidance regarding these derivatives, the derivatives are structurally related to the compounds recited in Claim 13. For example, the Specification states:

> "Derivatives" and "variants" of agents are agents which have been modified. They can, for example, include agents which have been modified by alterations in the amino acid sequence associated with the portions. They also include, but are not limited to, truncated and hybrid forms of agents. "Truncated" forms are shorter versions of agents. "Hybrid" forms are agents that are composed of portions of two or more agents, i.e., portions of one agent combined with portions of one or more other agents. (page 14, lines 21-26).

Moreover, the methods for production of derivatives were well known at the time of applicants' invention, and there was a high level of skill in the art of creation of protein derivatives at that time. Thus, the Specification provides adequate support for the scope of the claimed invention, articularly as the claims are amended.

The Examiner states that applicants should limit the costimulation blockade agents and derivatives to those set forth in Claim 13 and in the specification as filed to obviate this rejection. Claims 22-24 have been added. These claims are directed to compositions and kits comprising rapamycin, or a biologically active derivative thereof, and at least one costimulation blockade agent comprising at least one agent selected from the group of specific agents set forth in amended Claim 13. Derivatives are not recited in these claims. Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

Rejection of Claims 11-13 under 35 U.S.C. § 112, Second Paragraph

A) Claim 13 is rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, because the preamble

states "the method of claim 11" whereas Claims 11 and Claim 13 are drawn to compositions. Claim 13 has been amended to recite the "composition" of Claim 11.

B) Claims 11-13 are rejected as indefinite in that "the antecedent basis for 'a biologically active derivative thereof' is unclear (e.g., agent or rapamycin)." Claim 11 has been amended to clarify that the composition includes a biologically active derivative of rapamycin. Claims 12-13 are dependent upon Claim 13 and, therefore, contain the same limitation.

C) Applicants have specifically pointed out the support for these amendments in the preceding section entitled "Claim Amendments".

Reconsideration and withdrawal of these rejections to these claims are respectfully requested.

Rejection of Record of Claims 11, 13 and 14 under 35 U.S.C. § 102(e)

Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as anticipated by de Boer et al. (U.S. Patent No. 5,869,050 or 5,747,034). According to the Examiner, in both patents, De Boer et al. disclose compositions comprising at least B7-specific antibodies (and modified forms thereof) and immunosuppressive agents comprising rapamycin as well as formulations including oils. The Examiner states that "although the claims are drawn to the elected species [of] CD40L-specific antibodies, the [following] art rejections of record in parent application USSN 09/075,311 are set forth herein in the interest of compact prosecution, given the broad recitation of claimed compositions".

In response to the Restriction Requirement, Applicants have elected to prosecute anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L, and derivatives thereof and not B7-specific antibodies. Claims 11, 13 and 14 have been amended accordingly. De Boer et al. do not disclose these species. Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

Rejection of Record of Claims 11-14 under § 103(a)

Claims 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent Nos. 5,869,050 and/or 5,747,034) in view of Kelly et al. (U.S. Patent No. 5,118,493). According to the Examiner, De Boer et al. teach compositions comprising at least B7-specific antibodies (and modified forms thereof) and immunosuppressive agents comprising rapamycin as well as formulations including oils, and Kelly et al. teach the use of fish oils for immunosuppressive agents such as cyclosporin.

As stated above, applicants have amended Claims 11, 13 and 14 to be specifically directed to anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L, and derivatives thereof. Claim 12 depends upon Claim 11 and contains the same limitation. De Boer et al. do not disclose these species. Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

Rejection of Claims 11, 13 and 14 under 35 U.S.C. § 102(e)

Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as anticipated by Chen et al. (U.S. Patent No. 5,990,109). According to the Examiner, Chen et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin. The Examiner states that no more of the reference is required than that it sets forth the substance of the invention, and that the claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents.

Applicants respectfully disagree. Chen et al. do not disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents. They teach compositions comprising at least heterocyclo-substituted imidazopyrazine compounds and compositions, for use as protein tyrosine kinase inhibitors. In Column 21, paragraphs 1-3, cited by the Examiner, Chen et al. state that the compounds of the invention may be employed alone or in combination with each other and/or other suitable therapeutic agents (Column 21, lines 15-21). The exemplary agents listed include anti-agents blocking the interaction between CD40 and gp39 such as antibodies specific for CF40 [sic], fusion proteins constructed from CD40 (CD40Ig), and

rapamycin (Column 21, lines 22-37). Chen et al. do not disclose or claim compositions of such agents which do not also include heterocyclo-substituted imidazopyrazine compounds. Moreover, Chen et al. do not disclose kits of any kind.

Applicants' claimed compositions and kits do not comprise as active ingredients the heterocyclo-substituted imidazopyrazine compounds disclosed in Chen et al. Rather, the claimed compositions and kits comprise rapamycin and specific agents, namely anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L, and derivatives thereof, that applicants have demonstrated are effective for transplant tolerance without administered heterocyclo-substituted imidazopyrazine compounds as additional active agents.

Moreover, the Examiner states that, although the term "kit" is not specifically taught by the reference, there is no recitation that separates the prior art compositions comprising the same active ingredients as the instant claims. However, Chen et al.'s compositions do not comprise the same active ingredients as the instant claims. They comprise an additional active ingredient, heterocyclo-substituted imidazopyrazine compounds.

Therefore, Chen et al. do not anticipate the claimed invention. Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

Rejection of Claims 11, 13 and 14 under 35 U.S.C. § 102(e)

Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as anticipated by Nadler et al. (U.S. Patent No. 5,962,415). According to the Examiner, Nadler et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin.

Applicants respectfully disagree. Nadler et al. do not disclose compositions comprising CD40L-specific antibodies. Nadler et al.'s compositions comprise polypeptide inhibitors of nuclear translocation of a cytoplasmic protein and an immunosuppressant, such as rapamycin. (Column 1, lines 1-5; column 3, lines 6-25; column 14, lines 45-51). They disclose that proteins destined to be transported in the nucleus contain within their amino acid sequence a short stretch

of amino acids termed a nuclear localization sequence (NLS), which directs the transport of a protein from the cell cytoplasm across the nuclear envelope barrier. (Column 6, lines 20-23). The polypeptides of Nadler et al.'s compositions contain at least one such NLS and a signal sequence (an amino acid sequence that can deliver the polypeptide across the cytoplasmic membrane into the cell). (Column 3, lines 21-28; column 6, lines 8-14). Nadler et al. also disclose that the inhibition of immune responses by their compositions can take the form of inhibition of antibody production and inhibition of the expression of cell-surface receptors such as gp39 and CD40. (Column 8, lines 30-41).

Nadler et al. do not disclose applicants' compositions and kits comprising rapamycin, or a biologically active derivative thereof, and at least one costimulation blockade agent such as anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.

The Examiner states that no more of the reference is required than that it sets forth the substance of the invention, and that the claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents. However, the claimed functional limitations of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof are not the same as those of Nadler et al.'s polypeptide inhibitors of nuclear protein translocation.

Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

Rejection of Claims 11-14 under 35 U.S.C. § 103(a)

Claims 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noelle et al. (U.S. Patent No. 5,942,229) in view of Chen et al. (U.S. Patent No. 5,990,109) and/or Nadler et al. (U.S. Patent No. 5,962,415) and further in view of Kelly et al. (U.S. Patent No. 5,118,493).

According to the Examiner, Noelle et al. teach the coadministration of two immunosuppressive agents comprising CD40L-specific antibodies as well as art-known compositions and immunosuppressants. Noelle et al. teach combined administration of an

antagonist which interferes with the interaction of gp39 and CD40, and another immunosuppressive agent, such as a cytokine inhibitor, an inhibitor of the CD28/CTLA4 pathway or an immunosuppressive drug. (column 2, line 65 - column 3, line 4). Although Noelle et al. teach soluble CTLA-4 and inhibitors of IL-4 (for example, an anti-IL-4 antibody) as examples of immunosuppressive agents, they do not teach compositions or kits comprising rapamycin.

According to the Examiner, both Chen et al. and Nadler et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin. The Examiner also states that Kelly et al. teach the use of fish oils for immunosuppressive agents such as cyclosporine, and that, given the reduced nephrotoxicity associated with fish oils with immunosuppressive agents as taught by Kelly et al., one of ordinary skill in the art would have been motivated to select such fish oils as a suitable oil for immunosuppressive compositions and compositions taught by Noelle et al., Chen et al. and Nadler et al. in immunosuppressive regimens.

However, as noted above, neither Chen et al. nor Nadler et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents. Chen et al. teach compositions comprising at least heterocyclo-substituted imidazopyrazine compounds, for use as protein tyrosine kinase inhibitors, and Nadler et al. teach compositions comprising polypeptide inhibitors of nuclear protein translocation. These inhibitors do not share the same properties of Applicants' claimed costimulation blockade agents.

Neither Chen et al. nor Nadler et al. teach or suggest combining their compositions comprising rapamycin and their claimed compounds with the claimed CD40/CD40L antagonists. Conversely, Noelle et al. do not teach or suggest combining gp39 antagonists with rapamycin. In an obviousness analysis, a proposed modification of a prior art reference cannot change the principle of operation of the reference (M.P.E.P. § 2143.01). Here, the teachings of Chen et al. and Nadler et al. are focused on the mechanisms of specific compounds which are not the agents claimed by applicants. Moreover, there is nothing in the teachings of Noelle et al. and Kelly et

al. to provide a motivation to modify the compositions of Chen et al. and Nadler et al. to practice the claimed invention.

Therefore, one of skill in the art would not have been motivated to combine the teachings of Chen et al. (compositions comprising at least heterocyclo-substituted imidazopyrazine) or Nadler et al. (compositions comprising polypeptide inhibitors of nuclear protein translocation) with Noelle et al. (compositions comprising gp39 antagonists and cytokine inhibitors, inhibitors of the CD28/CTLA4 pathway or immunosuppressive drugs) or Kelly et al. (compositions comprising fish oil) with a reasonable expectation of success. Thus, the invention would not have been obvious at the time the invention was made to one of ordinary skill in the art.

Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

CONCLUSION

The claims are now in condition for allowance. Thus, the Examiner is respectfully requested to reconsider the rejections and to withdraw them.

If the Examiner feel that a telephone conversation with Applicants' attorney would be helpful in expediting the prosecution of this case, the Examiner is encouraged to call Applicants' Attorney at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Attorney for Applicants
Registration No.: 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742
Dated: March 25, 2002

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Please replace the paragraph at page 11, lines 16 through 25 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph:

By "administer" is meant to introduce to an animal, preferably a human. Agents and compositions can be administered sufficiently prior to transplantation to allow for the induction of a sufficient tolerance response to provide protection against rejection, but should not be administered so far in advance of the transplant that the degree of protection is inadequate to provide the prophylactic or therapeutic effect desired. This time frame is generally from one hour to one week, depending on the organism, and the conditions of administration. In another embodiment, an agent or composition may be administered during the transplantation procedure. Immunosuppressive and costimulation agents may be administered in single or multiple doses, which may be [adminsitered] administered continuously (repeatedly).

Please replace the paragraph at page 13, line 25 through line 14, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph:

Additionally, optionally, one or more agonistic or [antigonistic] antagonistic agents can be included in the compositions described herein, or can be administered before, during, or after administration of costimulation blockade agent or an immunosuppressive agent. An agonist or antagonist agent is an agent e.g., which enhances or prolongs the activity of an immunosuppressive or costimulation blockade agent, or one or more agents which aid in the uptake of an immunosuppressive or a costimulation blockade agent.

Please replace the paragraph at page 16, lines 5 through 14, with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph:

BALB/c mouse heart allografts were transplanted into C3H/He mice (Jackson Labs, Bar Harbor, Maine) with strong histocompatibility barriers, which were divided into six treatment groups of 5 mice each: treated with only costimulation blockade: anti-CD40 ligand monoclonal antibody (MR1, gift of Dr. M. Sayegh, Brigham and Women's Hospital, Boston, MA) and CTLA4-Ig (Steiner et al., J. Immunology (1995)); treated with the costimulation blockade plus cyclosporine (Sandoz [Pharamaceutical] Pharmaceutical Inc.); treated with the costimulation blockade plus rapamycin (Wyeth Research Institute, Princeton, NJ); treated with only cyclosporine; treated with only rapamycin; and untreated. A control group of three C3H/He mice received syngeneic transplants. The treatments were given as follows:

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

11. (Amended) A composition comprising rapamycin, or a biologically active derivative thereof, and at least one costimulation blockade agent [and rapamycin, or a biologically active derivative thereof], wherein the costimulation blockade agent comprises at least one agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.

13. (Amended) The [method] composition of Claim 11 wherein the costimulation blockade agent comprises at least one agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies,[anti-B7 antibodies, anti-CD28 antibodies, anti-CTLA4 antibodies, B7-Ig, CD28-Ig,] CD40-Ig, CD40L-Ig, [CTLA4-Ig;] and soluble

extracellular domain proteins of CD40[,] and CD40L [, B7, CD28 and CTLA4] and derivatives thereof[, and costimulation blockade drugs].

14. (Amended) A kit comprising at least one costimulation blockade agent and rapamycin, wherein the costimulation blockade agent comprises at least one agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.